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ARTICLE

Breast cancer management pathways during the COVID-19 pandemic: outcomes from the UK ‘Alert Level 4’ phase of the B-MaP-C study

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BACKGROUND: The B-MaP-C study aimed to determine alterations to breast cancer (BC) management during the peak transmission period of the UK COVID-19 pandemic and the potential impact of these treatment decisions.

METHODS: This was a national cohort study of patients with early BC undergoing multidisciplinary team (MDT)-guided treatment recommendations during the pandemic, designated ‘standard’ or ‘COVID-altered’, in the preoperative, operative and post-operative setting.

FINDINGS: Of 3776 patients (from 64 UK units) in the study, 2246 (59%) had ‘COVID-altered’ management. ‘Bridging’ endocrine therapy was used ($n = 951$) where theatre capacity was reduced. There was increasing access to COVID-19 low-risk theatres during the study period (59%). In line with national guidance, immediate breast reconstruction was avoided ($n = 299$). Where adjuvant chemotherapy was omitted ($n = 81$), the median benefit was only 3% (IQR 2–9%) using ‘NHS Predict’. There was the rapid adoption of new evidence-based hypofractionated radiotherapy ($n = 781$, from 46 units). Only 14 patients (1%) tested positive for SARS-CoV-2 during their treatment journey.

CONCLUSIONS: The majority of ‘COVID-altered’ management decisions were largely in line with pre-COVID evidence-based guidelines, implying that breast cancer survival outcomes are unlikely to be negatively impacted by the pandemic. However, in this study, the potential impact of delays to BC presentation or diagnosis remains unknown.

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BACKGROUND

COVID-19 impact in the United Kingdom

The first case of the novel coronavirus SARS-CoV-2 (coronavirus disease 2019, COVID-19) was confirmed in the United Kingdom on January 30, 2020.¹ As of August 4, 2020, COVID-19 has resulted in 17,918,582 confirmed cases and 686,703 deaths worldwide since its emergence in December 2019.² Globally, the COVID-19 pandemic has significantly impacted healthcare delivery, including alterations in cancer care. On 16th March, the UK’s lockdown response was initiated in response to the United Kingdom reaching ‘Alert Level 4’ (transmission high or rising exponentially), with advice against ‘non-

essential’ travel, social distancing and guidance on self-isolation.³ On 17th March, NHS England announced that all non-urgent operations in England would be postponed from 15th April to free up 30,000 beds.⁴ The ‘Alert Level 4’ subsided on 8th May, with the relaxation of the ‘stay at home’ message.

Management of breast cancer in the United Kingdom

There are 55,200 new breast cancer diagnoses per year, which represents 15% of all cancers diagnosed in the United Kingdom.⁵ Multi-modality treatment, including surgery, radiotherapy (RT) and systemic therapy, involves multiple hospital visits increasing the

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potential risk of exposure to COVID-19. With current treatments, early breast cancer prognosis is usually excellent.^{5,6} Compromises to cancer care during the COVID-19 pandemic as a result of rationalisation of resources and prioritisation of individual patient's cancer versus COVID-19 risks have the potential to impact on survival, as well as the quality of life (QoL), service provision and health economics.

Guidelines for the management of breast cancer during the COVID-19 pandemic

Multidisciplinary UK guidelines, as well as several European and American guidelines, were published early in the alert phase, informing management of breast cancer during the pandemic (Supplementary Tables 1 and 2).^{7–13} All aimed to assist rationalisation and prioritisation of delivery of breast services whilst healthcare resources were limited and hospitals were considered a high-infection risk environment. The majority of recommendations did not deviate substantially from pre-COVID National Institute for Health and Care Excellence (NICE) national guidance.⁶ Guidance emphasised multidisciplinary management, balancing the risk of COVID-19 infection during treatment and the burden of the COVID-19 pandemic on re-structured health services⁷ to enable the delivery of cancer care whilst safeguarding resources for patients with COVID-19 infection.

When theatre capacity was compromised, guidelines included the use of preoperative, or 'bridging', endocrine therapy (ET)¹⁴ and priority-driven management based on tumour biology^{10,13,15} (Supplementary Table 1) with the postponement of non-urgent surgery. Advice included reserving neoadjuvant chemotherapy (NACT)¹³ for non-operable disease only, careful consideration of the risk/benefit of chemotherapy and streamlined use of adjuvant radiotherapy (RT),¹⁶ including potential omission of breast or nodal radiotherapy or use of five-fraction radiotherapy (5F RT). The FAST-Forward trial results, published on April 28, 2020, demonstrated non-inferiority for local recurrence for 5F RT compared to the UK standard of care of 15 fractions (15F) and with improved early and similar late normal tissue toxicity,¹⁷ providing evidence for oncologically appropriate RT delivery in a reduced number of visits. There was a move towards creating 'green' operating capacity, defined as an operating theatre intended to be COVID-19 free (e.g., theatres geographically separate from patients treated for COVID-19, only doing elective cases with preoperative negative SARS-CoV-2 test as a requirement). This is in contrast to a 'red' site, defined as an operating theatre delivering emergency surgery in hospitals caring for COVID-19 patients or patients without a preoperative negative COVID test. In the United Kingdom, this involved either restructuring of hospital facilities or sourcing operative capacity in the independent sector.

With the aim of minimising surgical complexity, length of stay and complication risks, and therefore reducing the risk of COVID-19 infection, immediate breast reconstruction (IBR) was suspended, with delayed reconstruction to be offered once services returned to normal. In addition, breast units across the United Kingdom suspended breast screening from March 2020.

Aims and objectives

The aim of the B-MaP-C study was to determine (i) changes to breast cancer management during 'UK alert level 4' of the UK COVID-19 pandemic (March 16, 2020 to May 8, 2020),⁶ (ii) the potential repercussions of these changes to care in terms of oncological impact, quality of life (QoL) and healthcare costs and (iii) the impact of a concurrent COVID-19 diagnosis on patients undergoing treatment for breast cancer.

METHODS

A multicentre national cohort study was conducted in which consecutive patients with a diagnosis or early breast cancer

undergoing MDT-guided treatment recommendations during the peak of the COVID-19 pandemic were eligible for inclusion.¹⁸ Full study information is available on bmapc.org. Patients were identified prospectively by the local participating clinical teams during the UK's 'Alert Level 4' phase of the COVID-19 pandemic (defined as 16th March (the commencement of social distancing recommendations in the United Kingdom) to 8th May [relaxation of the 'stay at home' message]).

Data were collected and managed using REDCap™ electronic data capture tools hosted at The University of Manchester,¹⁹ in accordance with Caldicott II principles. Each participating unit was required to register the study locally with their hospital audit department and obtain local governance approvals prior to the commencement of data collection. Ethics approval was not required according to the NHS Health Research Authority online decision tool (www.hra-decisiontools.org.uk/research/).¹⁸

We collected patient demographic data, cancer-specific data and multidisciplinary treatment recommendations in the pre-operative, operative and post-operative setting. Patients on NACT prior to the pandemic could enter the study period at the peri- or post-operative multidisciplinary team meeting (MDT-M) (Fig. 1), hence the inclusion of patients having a diagnosis from August 1, 2019. For each management decision, collaborating units determined whether the decision was 'standard' (i.e., the same as would have been made pre-COVID) or 'COVID-altered', i.e., not standard management for that unit's usual practice (even if standard practice for other units). An example would be if a unit's standard practice is to perform axillary node clearance after positive sentinel node, but during the alert level 4 period, a patient was recommended no further axillary surgery after positive sentinel node.¹⁸ Hence, any alterations in management identified were as a direct result of the COVID-19 pandemic, representing treatment out of the ordinary for that collaborating unit. This allowed us to reflect the changes caused by the pandemic, whilst taking into account the background variability of practice across the United Kingdom. Altered management decisions were interrogated in more detail and compared to pre-COVID NICE guidance on breast cancer management⁶ as well as published COVID-specific guidelines.^{9,12,13,16,20}

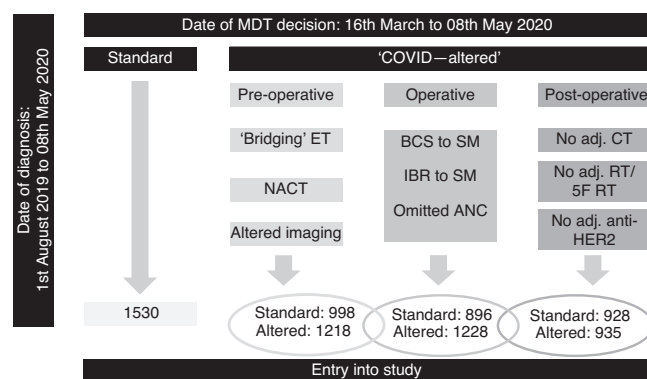


Fig. 1 Study schematic showing the points at which patients may enter into the study, the number of patients in each group and the timelines reported in the study. Patients may have 'standard' treatment at all stages in their management journey or may have 'COVID-altered' treatment. This latter group may have 'COVID-altered' management in the preoperative, operative or post-operative stage, and may indeed have 'standard' management decision at some stage. Overlapping ovals indicate overlapping sub-cohorts. ET endocrine therapy, NACT neoadjuvant chemotherapy, BCS breast-conserving surgery, SM simple mastectomy, Adj. adjuvant, CT chemotherapy, RT radiotherapy, HER2 human epidermal growth factor receptor.

Data analysis

The study was reported in accordance with the STROBE guidelines for observational studies.²¹ A pre-specified statistical analysis plan was approved by the study steering group. The descriptive analysis examined characteristics of those patients in whom standard management was followed and those with 'COVID-altered' management. The subsequent descriptive analysis explored patients' demographic and clinical characteristics within each altered management scenario. Continuous variables are presented by means (standard deviation, SD) or medians (interquartile range, IQR), categorical variables are presented by frequency (percentage). Calculations for each categorical variable were performed following the exclusion of missing values for this variable only. Non-parametric Mann-Whitney tests were performed to test for differences of medians between groups separately for each continuous and ordinal variable and Chi-squared tests for associations between nominal variables. To understand the national variation in the response to COVID-19, both in terms of MDT-M decisions and logistic arrangements, management decisions for the top 10 recruiting units (as exemplars) were compared. Analyses were computed using Stata MP (version 16). Where pertinent, the benefit of chemotherapy (without taking into account bisphosphonate treatment) using the *NHS Predict* online tool was calculated.²² Key exemplar healthcare costs (using unit costs from published databases [NHS Reference Costs and Supply Chain]) were compared between routine and 'COVID-altered' management to estimate potential financial impacts to the NHS (Supplementary Material).

Data validity

We utilised REDCap's built-in analysis tools to run tests of data completeness and consistency. In particular, the 'phased' data collection offered by the study design allowed us to perform validation checks to ensure consistency of data entry (Supplementary Table 3). Specifically, we calculated the percentage of concordance as the agreement of phases 1 and 2 of the study¹⁸ divided by total cases, for each category of 'COVID-altered' management.

RESULTS

There were 3776 patients included in the study from 64 breast units in the United Kingdom (with rapid data accrual and wide geographical representation from screening and symptomatic units and University Teaching Hospitals and District General Hospitals, Supplementary Fig. 1). Data validity tests showed high agreement in all fields interrogated, ranging from 95 to 99% (Supplementary Table 3). Of the patients included, 1530 (41%) had standard management and 2246 (59%) had 'COVID-altered' management at some point within their treatment journey. Patients with the higher-stage disease were statistically more likely to have 'standard' management (Table 1). Conversely, screen-detected cancers were more likely to have standard management, which may be a function of fewer screen-detected cancers being treated as the study period progressed (Fig. 2). Patients with 'COVID-altered' management had equivalent ER-positive disease (81%) and HER2-positive disease (12%) when compared to contemporary national data.²³

Breast cancer management decisions altered due to COVID-19: neoadjuvant treatment

Of the 2216 patients who had MDT-M decisions in the preoperative setting, 252 patients had omitted ($n=160$) or incomplete ($n=92$) NACT. For those 160 patients where the pandemic resulted in the omission of NACT, the majority (143/156 [92%]) went on to receive ACT.

To allow postponement of surgery, 951 patients had 'bridging' ET (defined in the protocol as 'Patient with hormone receptor-

Table 1. Patient demographics in the B-MaP-C study cohort.

	Standard management	'COVID-altered' management	P value	Total
	N = 1530	N = 2246		3776
Age (median-IQR)	56 (48–68)	60 (51–70)	<0.001	59 (50–69)
Missing	1	4		
T (n = 3682)				
Tis	119 (8%)	228 (10%)	<0.001	347
T1	577 (38%)	981 (45%)		1558
T2	609 (40%)	777 (36%)		1386
T3	159 (11%)	165 (8%)		324
T4	46 (3%)	21 (1%)		67
Missing	20	74		
N (n = 3666)				
N0/ N1mi	1037 (69%)	1665 (77%)	<0.001	2702
N1	318 (21%)	379 (18%)		697
N2	92 (6%)	74 (3%)		166
N3	63 (4%)	38 (2%)		101
Missing	20	90		
M (n = 3675)				
M0/MX	1493 (99%)	2149 (99%)	0.033	3642
M1	20 (1%)	13 (1%)		33
Missing	17	84		
WHO performance status (n = 3731)				
0	1215 (80%)	1688 (76%)	0.032	2903
1	187 (12%)	375 (17%)		562
2	76 (5%)	126 (6%)		202
3	36 (2%)	22 (1%)		58
4	6 (0%)	0 (0%)		6
Missing	10	35		
Presentation (n = 3716)				
Symptomatic	427 (28%)	913 (41%)	<0.001	1340
Screen-detected	1072 (72%)	1304 (59%)		2376
Missing	31	29		

T tumour stage, N nodal stage, M metastases, WHO World Health Organisation.
T, N are pathological TNM, except where patients were having ET/NACT, in which case TNM is taken from imaging, using T stage based on the largest reported size from all imaging modalities.
M1 = patients who were diagnosed with metastatic disease after surgery.

positive cancer having 'bridging' endocrine therapy due to a potential delay in surgery), of which the vast majority (708/862, 82%) were postmenopausal (Table 2). Of patients commenced on ET, 740/774 (96%) were strongly ER-positive (Allred score 7–8), with only 4/774 (<1%) having a score below 5, and 140/900 (15%) assessed pre-operatively as node-positive. Although the primary reason for 'bridging' ET is likely due to anticipated reduced theatre capacity, in some, the decision may have been driven by comorbidity and increased risk of COVID-19 mortality.

Surgery

Preoperative imaging assessment was altered in 50 patients, for example with the omission of magnetic resonance imaging to assess disease extent. Of the 957 patients with altered surgical recommendations, 589/957 (62%) had breast-conserving surgery (BCS), 356/957 (37%) had a simple mastectomy and 12/957 (1%) had a mastectomy with IBR. There were 42 patients who had a simple mastectomy when BCS was clinically possible (defined in the protocol as MDT recommendation for simple mastectomy over BCS influenced by potential unavailability of radiotherapy),

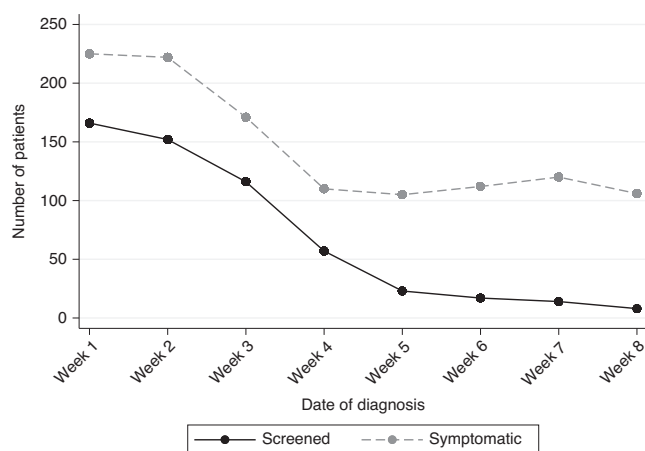


Fig. 2 Change over time in the number of patients presenting with screen-detected versus symptomatic breast cancer during the study period. Week 1 begins on 16th March, and week 8 ends on 8th May.

likely because breast radiotherapy could not be delivered locally. This group had a high number of premenopausal patients (13/40, 33%), with high-grade disease (26/41, 63% grade 3) and disproportionately more ER-negative disease (17/41, 41%) (Table 2), suggesting that oncological considerations impacted these decisions. Thirteen patients had change to standard practice because they had no completion axillary clearance (ANC) following a positive sentinel node, when ANC at that unit would have been offered pre-COVID. There is relative clinical uncertainty around completion ANC in subgroups of patients. For example, based on pre-COVID advice, all 13 patients were eligible for the POSNOC study²⁴ where ANC could have been appropriately omitted. Nine patients also fulfilled Z0011 criteria for the omission of completion axillary clearance.²⁵

The utilisation of IBR has doubled over the last two decades.²⁶ However, in this cohort, there were 299 patients who were not offered IBR, when the usual pre-COVID practice would have included this. These patients were young (median age 50, 61% premenopausal), reflecting a subgroup where IBR would usually be considered a priority. The estimated cost of mastectomy and IBR for these patients would have been £1,636,969, whereas the total cost of mastectomy plus delayed reconstruction is an estimated £3,063,428 (an additional cost of £1,426,459; Supplementary Material).

Adjuvant treatment

Of 1863 patients who had a post-operative MDT-M decision, 81 patients had adjuvant chemotherapy omitted, which would have been offered in the pre-COVID environment, including 13/81 patients with omitted NACT as described above. There were 62/81 patients in whom a decision was made to omit chemotherapy based on clinical grounds (without genomic testing). This group had a median benefit of chemotherapy of 3% (IQR 2–9%) using NHS Predict calculations.²² The majority of patients with omitted chemotherapy were postmenopausal (61/80, 75%), with no/low nodal burden (N0 or N1 = 77/80, 96%) and ER-positive disease (59/81, 73%) with one or more comorbidities (80/81, 99%), implying holistic risk-benefit decision-making (Table 2). Collaborating units were asked to report cases where genomic testing directly influenced MDT-M recommendation to avoid adjuvant chemotherapy (that, following NICE guidance, would not usually have been used pre-COVID). This was the case in 19/81 patients. In addition, extended-indication genomic testing outside of the 2018 NICE guidelines (such as patients with node-positive disease,

which was outside of NICE guidance),²⁷ was used in 27 patients, of whom 21 avoided chemotherapy based on genomic test outcome.

Thirteen patients with HER2-positive disease had no adjuvant-targeted (anti-HER2) therapy or chemotherapy when standard management would have included this. The median age of this group was 73 (range 52–84), with low tumour stage (T1 = 5/13, T2 = 7/13), low nodal stage (N0/N1 = 11/13) and largely ER-positive disease (11/13). Four patients with HER2-positive disease received adjuvant anti-HER2 therapy without systemic adjuvant chemotherapy, in accordance with COVID-19 guidance.

There were 96 patients in whom adjuvant radiotherapy was not recommended, whereas pre-COVID local MDT-M practice would have been to recommend radiotherapy. We explored the clinicopathological characteristics of these patients and noted that of these 96, 45 patients (47%) met inclusion criteria for the avoidance of radiotherapy based on NICE guidelines⁶ or the PRIME2 study.²⁸ In line with the time guidelines for 5F breast and chest wall RT¹² and the FAST-Forward publication, 781 patients had adjuvant radiotherapy with 5F where, pre-COVID, 15F would have been administered (Table 2). Of 64 units included in this study, 46 (72%) offered the fast-forward radiotherapy protocol, evidencing the ability to rapidly introduce new clinical practice based on high-quality trial data. As an exemplar of the potential positive health economic impact of changes to management, the cost saving of change to 5F was investigated. The change from 15F to 5F for these patients is estimated to have saved £1,421,420 (supplementary material). Compared to those having 5F RT, 504 patients receiving 15F were younger (median age 56 years, IQR 49–67 vs 59 years, IQR 53–67, $P = 0.006$), had larger tumours (mean size 27.6 mm (1.1) vs 20.3 mm (0.6), $P = 0.0000$), and higher nodal burden (mean number of macrometastatic nodes 2.3 (0.2) vs 0.4 (0.1), $P < 0.0001$).

Logistic changes to breast surgery during the COVID-19 pandemic Of 3776 patients, 1778 (47%) had surgery within the study period; 1052 (59%) were in 'green' (COVID low-risk) zone operating theatre and 726 (41%) in 'red' (COVID high-risk) theatres. There was a move towards increasing access to 'green' theatres as the study progressed as units adapted their services in response to the pandemic, from 51 (29%) operations in the first week to 125 (69%) operations in the final week of the study (Fig. 3). The median time to surgery from diagnosis for patients (excluding those on NACT or ET) was 24 days (IQR 16–34), and was similar in both 'red' (25 days, IQR 15–33) and 'green' (24 days, IQR 16–34) theatres, which is within NHS Breast Screening Programme/NICE pre-COVID targets.

Recommended practice for sentinel lymph node biopsy surgery is with dual localisation using Technetium-99m isotope and Patent blue dye.²⁹ In 122 cases, sentinel node biopsy was performed with blue dye only. This was more common in 'green' theatres that were usually non-NHS independent sector hospitals (117/122, 96%) versus 'red' theatres that were usually NHS acute care trusts (5/122, 4%).

Breast cancer management decisions: national variation

To get a sense of the variation in practice across the United Kingdom, we compared changes to normal practice in the ten units contributing the most patient datasets to the study (totalling 37% of the study cohort), with the frequency of 'standard' treatment, use of 'bridging' ET and use of five-fraction RT as exemplars. Within these ten units, the frequency of standard treatment ranged from 25% to 59%, the frequency of ET from 2% to 35% and of five fractions of RT from 11% to 51% of each hospital's total patient cohort (Fig. 4a). This may highlight local differences in the ability to access theatre space or to rapidly implement a new evidence-based practice. There was an increase in the number of patients having 'standard' treatment and less use

Table 2. Patient and cancer-specific data for patients having selected major COVID-altered management decisions.

N	Patients having omitted/incomplete NACT 252 ^c	Patients having 'Bridging' ET 951 ^c	Patients undergoing simple Mx when BCS possible 42 ^c	Patients not offered immediate breast reconstruction 299 ^c	Patients not having adjuvant CT 81 ^c	Patients not having adjuvant RT 96 ^c	Patients having five fractions RT 781 ^c
Age ^a	52 (28–78)	65 (35–92)	59 (39–77)	50 (28–75)	63 (38–78)	69 (63–77)	59 (53–67)
Menopausal status (n)							
Pre/peri-menopausal	121 (50)	154 (18)	13 (33)	176 (61)	20 (25)	13 (15)	187 (26)
Postmenopausal	119 (50)	708 (82)	27 (67)	113 (39)	61 (75)	76 (85)	544 (74)
Missing	12	89	2	10	0	7	50
Tumour stage							
Is	0	87 (10)	0	23 (8)	0	16 (17)	46 (6)
1	58 (23)	455 (50)	15 (37)	80 (27)	33 (41)	57 (61)	433 (56)
2	142 (57)	310 (34)	23 (56)	132 (44)	39 (49)	15 (16)	252 (33)
3	40 (16)	50 (6)	2 (5)	58 (20)	6 (8)	4 (4)	40 (5)
4	10 (4)	4 (0)	1 (2)	4 (1)	2 (2)	2 (2)	3 (0)
Missing	2	45	1	2	1	2	7
Nodal stage							
0/mi	125 (50)	760 (84)	23 (56)	175 (59)	36 (45)	82 (86)	638 (83)
1	75 (30)	124 (14)	14 (34)	76 (26)	41 (51)	12 (13)	112 (15)
2	33 (13)	10 (1)	4 (10)	32 (11)	3 (4)	1 (1)	15 (2)
3	17 (7)	6 (1)	0 (0)	14 (5)	0 (0)	0 (0)	6 (1)
Missing	2	51	1	2	1	1	10
Metastases							
M0	248 (99)	897 (100)	41 (100)	293 (99)	80 (100)	95 (100)	770 (100)
M1	2 (1)	3 (0)	0 (0)	3 (1)	0 (0)	0 (0)	3 (0)
Missing	2	51	1	3	1	1	8
Size	MMG/USS	MMG/USS	MMG/USS	MMG/USS	Path.	Path.	Path.
Size in mm ^b	29.0 (1.2)	20.7 (0.5)	24.2 (2.2)	32.8 (1.5)	27.5 (1.8)	17.8 (1.4)	20.3 (0.6)
Missing	9/8	34/39	1/1	13/9	1	3	20
Histological type							
IDC	226 (92)	599 (65)	39 (95)	207 (71)	65 (82)	65 (71)	548 (72)
ILC	7 (3)	149 (16)	0 (0)	48 (16)	8 (10)	5 (5)	107 (14)
Mixed	4 (2)	31 (3)	1 (2)	9 (3)	3 (4)	1 (1)	26 (3)
Other	9 (4)	54 (6)	1 (2)	6 (2)	3 (4)	5 (5)	40 (5)
DCIS	0	94 (10)	0	232 (8)	0	16 (17)	45 (6)
Missing	6	24	1	6	2	1	15
Grade (invasive)							
1	2 (1)	204 (25)	1 (2)	14 (5)	3 (4)	19 (26)	126 (18)
2	67 (27)	507 (62)	14 (34)	147 (54)	42 (53)	43 (58)	407 (57)
3	178 (72)	109 (13)	26 (63)	110 (41)	35 (44)	12 (16)	181 (25)
Missing	5	37	1	5	1	3	67
Grade (DCIS)							
LG	0	12 (14)	0	1 (4)	0	0 (0)	0 (0.0)
IG	0	29 (33)	0	5 (23)	0	4 (27)	12 (27)
HG	0	46 (53)	0	16 (73)	0	11 (73)	33 (73)
Missing	0	7	0	1	0	1	0
ER							
+	121 (49)	922 (100)	24 (59)	221 (76)	59 (73)	76 (89)	656 (86)
–	127 (51)	3 (0)	17 (41)	71 (24)	22 (27)	9 (11)	104 (14)
Missing	4	26	1	7	0	8	21

Table 2. continued

N	Patients having omitted/incomplete NACT 252 ^c	Patients having 'Bridging' ET 951 ^c	Patients undergoing simple Mx when BCS possible 42 ^c	Patients not offered immediate breast reconstruction 299 ^c	Patients not having adjuvant CT 81 ^c	Patients not having adjuvant RT 96 ^c	Patients having five fractions RT 781 ^c
PR							
+	78 (33)	620 (85)	19 (48)	160 (63)	48 (66)	51 (72)	462 (71)
—	155 (67)	106 (15)	21 (52)	95 (37)	25 (34)	20 (28)	188 (29)
Missing	19	225	2	44	8	21	221
HER2							
+	116 (47)	63 (8)	8 (20)	71 (26)	21 (26)	3 (4)	85 (12)
—	132 (53)	761 (92)	33 (80)	205 (74)	59 (74)	75 (96)	636 (88)
Missing	4	137	1	23	1	15	60
Ki67 ^b	36.2 (3.6)	18.8 (2.5)	29.6 (5.1)	27.4 (3.4)	24.4 (6.0)	14.6 (2.5)	19.8 (1.6)
Missing	213	847	24	246	65	75	654
Comorbidities							
None	6 (2)	46 (5)	1 (2)	6 (2)	1 (1)	4 (4)	19 (2)
≥1	246 (98)	905 (95)	41 (98)	293 (98)	80 (99)	92 (96)	762 (98)
Missing	0	0	0	0	0	0	0
WHO PS							
0	197 (79)	667 (71)	28 (67)	261 (87)	63 (78)	61 (64)	658 (85)
1	40 (16)	180 (19)	9 (21)	29 (10)	14 (17)	26 (27)	104 (13)
2	11 (4)	74 (8)	5 (12)	9 (3)	4 (5)	7 (7)	13 (2)
3	2 (1)	13 (1)	0 (0)	0 (0)	0 (0)	2 (2)	2 (0)
4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	2	17	0	0	0	0	4

NACT neoadjuvant chemotherapy, ET neoadjuvant endocrine therapy, Mx mastectomy, BCS breast-conserving surgery, CT chemotherapy, RT radiotherapy, IDC invasive ductal carcinoma, ILC invasive lobular carcinoma, DCIS ductal carcinoma in situ, LG low grade, IG intermediate grade, HG high grade, ER oestrogen receptor, PR progesterone receptor, HER2 Human epidermal growth factor receptor 2, PS performance status.

^aMedian (IQR).

^bMean (SD).

^cPatients could be in more than one category.

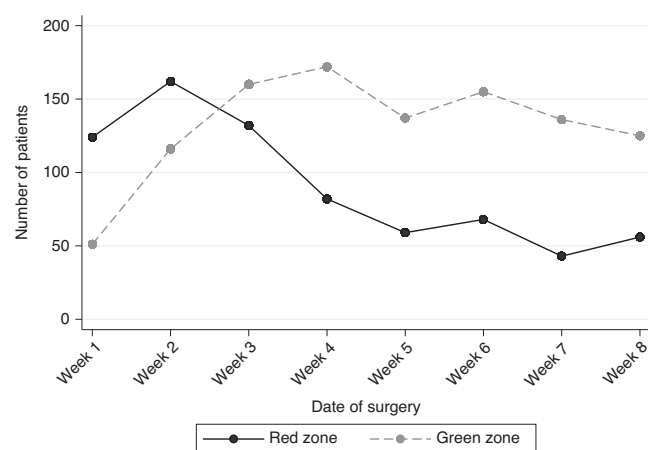


Fig. 3 Transition to 'green' (COVID low-risk) theatres. Change over time during the 'study period, showing an increase in the number of operations performed in a 'green' (COVID low-risk) versus 'red' (COVID high-risk) zone.

of 'bridging' ET as the study progressed (Fig. 4b), indicating some recovery in service delivery. In patients commenced on pre-operative/'bridging' ET, 210 patients went on to have surgery by the end of the study. The median length of time of ET for these

patients was 22 days (IQR 15–31). The most common reason for proceeding with surgery early was unexpected availability of theatre capacity (53%).

SARS-CoV-2 testing, outcome and impact on patient journey
There were 1392 patients tested for SARS-CoV-2, the majority in the preoperative setting (1033, 74%). Fourteen patients tested positive (1%). Of 11 patients testing positive before surgery, all were managed at home, without need for hospital admission, with a median time from diagnosis to surgery of 52 days (range 18–168). Those with >90-day delay ($n = 2$) were temporised with 'bridging' NET. There was an increase in preoperative hospital testing during the study period, no doubt, reflecting the increasing availability of SARS-CoV-2 tests nationally (Supplementary Fig. 2). Three patients tested positive post-operatively, of which two had surgery in a red zone.

There was no SARS-CoV-2-related mortality.

DISCUSSION

The COVID-19 pandemic has had unprecedented effects on healthcare provision across the United Kingdom. Early reports from both the United Kingdom and globally have shown that malignancy was a predictor of mortality^{30,31} and poor outcomes from COVID-19.^{31–33} No previous reports have focused specifically on alterations of care during the pandemic, to early breast cancer patients.³⁴ The major challenges during the pandemic have been to weigh treatment benefit against potential transmission risk of

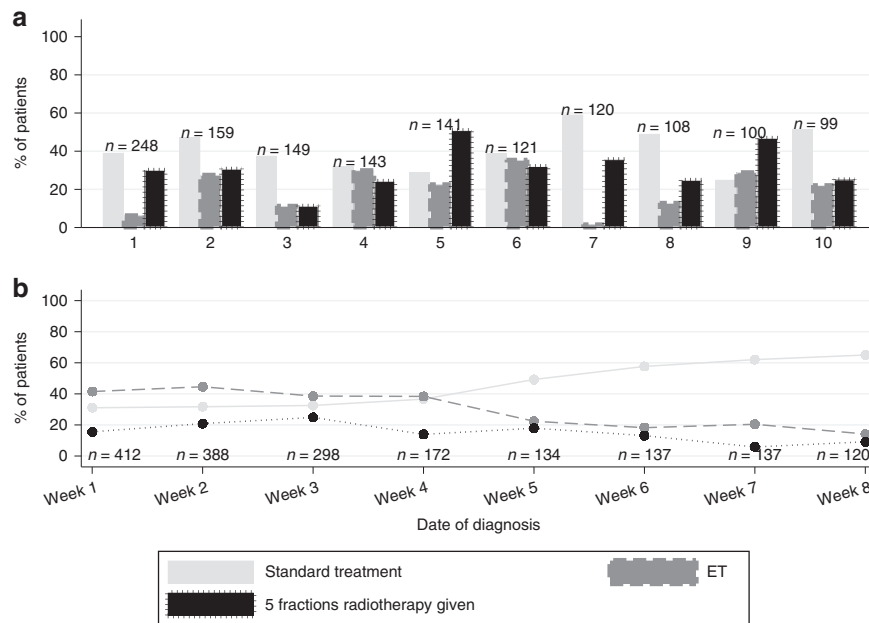


Fig. 4 National Variations in management of breast cancer during the COVID-19 pandemic. **a** Variation in management decisions in the top 10 recruiting units, comparing the percentage of patients with (i) standard management (light grey bar), (ii) bridging ET (grey bar) and (iii) 5-fraction RT (black bar). **b** Trends in management decisions during the study period, by date of diagnosis at weekly intervals.

SARS-CoV-2 to patients and healthcare providers, and to administer treatment in healthcare settings where resources and capacity are strained. The rapid publication of guidelines by several organisations^{7–13,16} facilitated the implementation of practical evidence-based decisions, as evidenced by the results of this study.

Despite treatment recorded as 'COVID-altered' in 2246 (59%) patients as per study definitions,¹⁸ the vast majority of patients in this study were treated according to pre-COVID guidelines. Only 439/2246 (19%) patients had a management that was clearly outside the pre-COVID breast cancer NICE guidelines (omission of a reconstruction or premenopausal patients on 'bridging' ET), implying that breast cancer oncological outcomes in this study are unlikely to be negatively impacted (although the psychological impact of reconstruction omission is yet to be determined). Where 'COVID-altered' management plans had to be instigated, these were mostly within guidelines published during the pandemic. There is likely, however, to be a cohort of women who are yet to present, either symptomatically or through screening, with breast cancer. Their outcomes may be disadvantaged through the late presentation, although that group lies outside the scope of this study.

Where theatre capacity has been an issue, there was increased use of preoperative ET compared to the usual pre-COVID practice,²⁹ largely as 'bridging' therapy.³⁵ Indeed, a large number of patients initially placed on 'bridging' ET in anticipation of significant surgical delay who have already had surgery, as theatre capacity, particularly in 'green' theatres, has increased. In those not receiving any neoadjuvant or bridging treatment ($n = 1074$), surgery has taken place in a timely manner. This has to be taken in context with the reduction in a number of patients presenting, particularly with screen-detected cancer. It is noteworthy that there were low rates of SARS-CoV-2 infection and no reported COVID-19-related post-operative deaths.

It is evident that some surgical decisions have reflected local resource availability for adjuvant therapies. For example, there was a cohort of patients ($n = 42$) undergoing simple mastectomy when pre-COVID practice would have been BCS followed by

adjuvant RT. These patients were younger, with more aggressive tumour characteristics, and hence this represents, for a short period of time, a decision to prioritise reduction of recurrence risk, whilst there was uncertainty over RT availability. We have identified a large group of patients who have not had IBR when usual practice would have recommended this. UK NICE guidelines recommend all women undergoing a mastectomy be offered IBR.⁶ However, the COVID-19 pandemic has led to the suspension of IBR in many countries worldwide due to resource, workforce and safety concerns. This may lead to detrimental effects on the aspects of QoL such as body image.

Internationally, standard-of-care chemotherapy treatment regimens have been adapted to minimise the intensity of hospital visits and hospitalisation, and to prevent cancer treatment-induced complications of COVID-19.^{7–11,13,15,16,20,36} Transferring NACT to the adjuvant setting is oncologically safe,³⁷ but may deprive the patient of the opportunity of downstaging to accommodate BCS, and prevent identification of nonresponders. These nonresponders may potentially be deprived of further adjuvant treatment such as the NICE-approved Trastuzumab emtansine in patients with HER2-positive disease or Capecitabine in patients with triple-negative breast cancer. The majority of patients omitting NACT received adjuvant chemotherapy reflecting the changing scenario during the COVID-19 'Alert Level 4', where initial apprehension for systemic therapy had subsided by the time these patients had completed surgery.

In many units, there has been rapid adoption of the results of the FAST-Forward study, with an almost immediate change to treatment protocols across the country.³⁸ We categorised 5F RT as 'altered management' because the start of the study predated the 5-year local control results of the FAST-Forward study, although prepublication national guidelines supported the use of 5F based on 3-year toxicity results of FAST Forward.¹² This allowed us to determine the reactivity of breast cancer services to new evidence and guidance issued during the pandemic. The 5F protocol was advantageous from a service provision perspective, where at the height of the pandemic, the workforce was greatly reduced, as well as from a safety viewpoint, given the reduced

number of hospital visits and COVID-19 exposure risk. For those that did not have adjuvant radiotherapy, most were within criteria for planned avoidance of radiotherapy using NICE guidelines⁶ and PRIME2²⁸ criteria. Had research trials been available, these patients may potentially have been recruited into the PRIMETIME study, which had been temporarily closed during the pandemic.

Inevitably, there are some limitations to a study of this nature, particularly one executed in such a short time frame. It is recognised that the data reported in this study have the potential to be subject to reporting bias, data entry error, and indeed, some decisions made early in the COVID-19 'alert level 4' may have been subject to change particularly as the peak of the pandemic subsided. It is also appreciated that the study did not include all units in the United Kingdom, and not all participating units were able to collect data on consecutive patients within the study period, by the study deadline. Nevertheless, this still remains a representative national picture of the impact of the COVID-19 pandemic on breast cancer treatment in the United Kingdom.

Clinical research is a key component of high-quality breast cancer care. In the year 2018/19, over 9000 patients were recruited to breast cancer clinical trials (National Cancer Research Institute Annual Report 18/19). However, the pandemic has resulted in the suspension of many clinical trials, with the redeployment of cancer research staff to allow prioritisation of COVID-19 studies. Across all cancer sites, only 31% of cancer trials continued as planned during the pandemic (National Institute for Health Research (NIHR), personal communication, unpublished data). Although the NIHR has now published a framework for restarting clinical research, recovery of trial recruitment is slow. This has implications for patients in accessing trials and novel treatments, and for researchers to deliver studies to time and target. The extent of this impact on the UK breast cancer clinical research portfolio, however, remains to be elucidated.

Our study has described the extent of changes (and key cost implications) in the management of breast cancer in the United Kingdom during the COVID-19 pandemic on a patient and population-based level, as a response to timely and feasible guidance that was largely followed at a time of national crisis. Appraisal of these changes will guide the evaluation of the impact of the pandemic on immediate patient outcomes and the degree to which breast cancer management has been affected in routine clinical practice. This will assist with planning of service delivery once routine breast cancer management resumes and in the event of a further pandemic. There are significant implications for the COVID-19 'recovery' phase with patients on endocrine therapy requiring cancer resection, and those denied IBR awaiting delayed breast reconstruction. Anticipating the recommencement of breast screening, this delayed (or postponed) activity is likely to overstretch breast surgical services. In the long term, we will have the opportunity to assess the impact of treatment alterations on the rate of disease recurrence and overall patient survival, QoL and the impact of these management decisions on the service and health economics.

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AUTHOR CONTRIBUTIONS

R.V.D. conceived the study. R.V.D., B.K., R.I.C., A.G. and C.C.K. designed the pilot study. R.V.D., B.K., A.C., R.O.C. and T.R. designed and trialled the pilot data collection forms. R.V.D., B.K., A.C., R.O.C., T.R., V.P.T., J.J.K., E.M.C., P.F., N.S., C.W.J.C., K.H., S.A.M., D.R.L., R.V., S.P., C.H., E.C., C.E.C., R.I.C., A.G. and C.C.K. contributed to the final study design and finalised data collection forms. A.C., R.V.D., R.O.C. and T.R. designed the study website, and coordinated collaborator recruitment and provided collaborator support. R.V.D., B.K., K.H., P.F., N.S., C.W.J.C., R.V., S.P., S.A.M., D.R.L., C.H., E.C., C.E.C., R.I.C., A.G. and C.C.K. provided clinical leadership and promoted unit participation and data collection. V.P.T., J.J.K. and E.M.C. provided methodological support. R.V.D., V.P.T., J.J.K. and E.M.C. drafted the statistical analysis plan and analysed the data. All authors contributed to data interpretation. R.V.D. led the study and wrote the first draft of the paper, with support from B.K., J.J.K., K.H., S.A.M., R.I.C., A.G. and C.C.K. All authors reviewed and critically revised the paper and approved it before submission.

ADDITIONAL INFORMATION

Ethics approval and consent to participate Ethics approval was not required according to the NHS Health Research Authority online decision tool (www.hra-decisiontools.org.uk/research/).

Data availability Data supporting the results reported in the paper cannot be found on publicly available databases. The data have been uploaded by collaborators onto a RedCap database, and individual units have access to their own data, but not the overall national data.

Competing interests The authors declare no competing interests. R.V.D., B.K., A.C., R.O.C., V.P.T., R.V., J.J.K., P.F., N.S., C.W.J.C., K.H., S.P., A.G., S.A.M., E.M.C., D.R.L. and C.H. have nothing to declare. Dr Tim Rattay (T.R.) is currently an NIHR Clinical Lecturer. Charlotte E Coles (C.E.C.) is supported by the National Institute Health Research Cambridge Biomedical Research Centre. Ramsey I Cutress (R.I.C.) has equipment provided by Seca to analyse body composition to University Hospital Southampton as part of an NIHR model industry collaborative agreement (MiCA). This equipment is used in an Academic Investigator-led charity-funded study of which Ramsey Cutress is Cl. Ellen Copson (E.C.) declares honoraria from Roche, Pfizer, Astra-Zeneca, Lilly, Nanostring and expert panel work for World Cancer Research Fund. Cliona C. Kirwan (C.C.K.) is Royal College of Surgeons/University of Manchester Professor of Surgical trials funded by a Royal College of Surgeons of England/Masonic Charitable Foundation professorship.

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